

(4163) Ochsner

"The probable significance between the increase in smoking and the increase in pulmonary malignancy has been previously emphasized by the authors. Numerous investigators have repeatedly demonstrated the irritating carcinogenic effect of tobacco. Roffo, on the basis of his extensive investigations, is convinced that tobacco is one of the most important carcinogenic agents. He has been able to produce tumors in rabbits as easily with tobacco tar as with coal tar. Hoffmann is 'strongly of the opinion that a relation between increase in smoking habits and cancer of the lung may be safely assumed to exist.' We found a significant relationship between the increased incidence of carcinoma of the lung in the United States and the increased production of tobacco." page 389, (4163)

(4164) Ochsner & DeBakey

"In a previous publication we called attention to the possible etiologic relation between the increase in smoking, with the universal custom of inhaling, and the increase in pulmonary carcinoma. The inhalation of smoke constantly repeated over a long period produces a chronic irritation of the bronchial mucosa, as is evinced by the characteristically associated cough. As early as 1923, Fahr stated that in his opinion the increase in the incidence of pulmonary carcinoma was due to the increased incidence of cigarette smoke. Lickint also expressed the opinion that the inhalation of tobacco smoke is a responsible factor in the increase of bronchogenic carcinoma and that such carcinoma in many cases can be prevented by abstinence from smoking, particularly by patients belonging to families known to have a high cancer incidence. Tylecote stated: 'In almost every case I have seen and known of the patient has been a regular smoker, generally of cigarettes.' McNally expressed the opinion that the tar of cigarette smoke may account for the recorded increase of cancer of the lung. Mertens has also expressed this view. Bogen and Loomis stated that the only woman with cancer of the lung on whom autopsy was done at the Olive View Sanatorium had smoked cigarettes excessively for more than fifteen years.

It is our definite conviction that the increase in the incidence of pulmonary carcinoma is due largely to the increase in smoking, particularly cigarette smoking, which is universally associated with inhalation. Every one of our patients, with the exception of 2 women, was

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**an excessive smoker. Of particular interest in this connection is the comparison of the death rate per hundred thousand of population from cancer of the lung with the production of tobacco and automobiles in the United States during the seventeen year period 1920 to 1936 inclusive. It may be observed from a graphic representation of these incidences that, whereas there is no significant relation between the production of automobiles and cancer of the lung, there is an obvious parallelism between the increased production of tobacco and carcinoma of the lung."** pages 219-221, (4164)

Note: All citations by Ochsner were collected and six were reviewed in Chapter III.

(4468) Ochsner, Dixon & DeBakey

"Whereas there are a number of factors which are responsible for the increased incidence of bronchiogenic carcinoma, it is our firm belief, as we have emphasized in previous publications, that the increased incidence is due to the greater frequency of smoking. Inhalation of smoke constantly repeated over long periods produces chronic irritation of the bronchial mucosa as is evidenced by the characteristically associated cough. Experimentally, the carcinogenic effect of tobacco has been demonstrated repeatedly. Roffo stated the conviction, on the basis of his clinical observations of 78,000 patients treated in the University Institute of Experimental Medicine for the Study of the Treatment of Cancer in Buenos Aires, that tobacco is the most important factor in determining the localization of cancer. He was able to produce carcinoma by applying tar derived from various tobaccos. Hoffman, on the basis of his statistical analyses of the incidence of cancer, states, 'Smoking habits unquestionably increase the liability of cancer of the mouth, the throat, the esophagus, the larynx, and the lung. The change in the cancer death rate during recent years has not, however, been at all disproportionate to the enormous increase in cigarette smoking habit which has replaced the older method of smoking, unquestionably, more injurious than smoking cigars. The increase in cancer of the lung observed in this and many other countries is in all probability to a certain extent directly traceable to the common practice of cigarette smoking and inhalation of cigarette smoke. The latter factors unquestionably increase the danger of cancer development.'" page 29, (4466)

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(4555) Ochsner, Dixon & DeBakey

"We have repeatedly emphasized the probable relationship between smoking and the increased incidence of bronchiogenic carcinoma. The chronic irritation resulting from the inhalation of cigarette smoke over long periods of time is well known and the chronic bronchitis in smokers is so common that their cough is considered inconsequential and of no significance. Whereas prolonged chronic irritation of the bronchial mucosa as a result of inhalation of smoke can in itself be a factor in the production of neoplastic disease just as any prolonged and continued irritation can produce such a lesion, it is probable that smoking exerts an additional and more active influence than chronic irritation alone. Experimentally, it has been demonstrated that tobacco exerts a carcinogenic effect." pages 1198-1199, (4555)

(4556) Ochsner

"It has also been suggested that the inhalation of exhaust gases from automobile engines might be a factor in the production of cancer of the lung. We have shown, however, that there is no parallelism between the sale of automobile tags and the incidence of lung cancer. On the other hand, there is a distinct parallelism between the incidence of cancer of the lung and the sale of cigarettes, and it is our belief that the increased incidence of lung cancer is due to the increased incidence of smoking and that smoking is a factor because of the chronic irritation that it produces. It is well known that the smoker has a chronic cough, the so-called smoker's cough, which because of its irritation might alone be responsible for the development of lung cancer. However, in addition to this it has been shown by Professor Roffo, Director of the Institute for Malignant Disease in Buenos Aires, tobacco contains a tar which has a carcinogenic effect and that the application of this tar to the skin and the mucous membrane of the respiratory tract in animals will produce cancer." page 105, (4556)

(4557) Ochsner, Dixon & DeBakey

"Etiology: Whereas there are a number of factors which are responsible for the increased incidence of bronchiogenic carcinoma, it is our firm belief, as we have summarized in previous publications, that the increased incidence is due chiefly to the greater

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frequency of smoking. The repeated inhalations of smoke over long periods produce chronic irritation of the bronchial mucosa as evidenced by the characteristically associated cough. As early as 1923, Fahr stated that in his opinion the increase in incidence of pulmonary carcinoma was due to the incidence of cigarette smoking. Lickint also expressed his opinion that the inhalation of tobacco smoke is a responsible factor in the increase of bronchiogenic carcinoma and that such carcinoma in many cases can be prevented by abstinence from smoking, particularly by patients whose families have been known to have a high cancer incidence. That smoking is of etiologic significance has been emphasized by Tylecote, McNally, Mertens, Bogen and Loomis." pages 101-102, (4557)

(4651) Ochsner

"Although the exact cause of cancer is not known, it is well accepted by medical authorities that chronic irritation over long periods of time will produce changes in the cells which are irritated, and this abnormal overgrowth of cells results in cancer. It is also well known that cigarette smoking with the inhalation of the smoke results in chronic irritation of the bronchial tubes as evidenced by the so-called smoker's cough, and it is reasonable to assume that this irritation alone over many years' time might be responsible for the development of cancer of the lung. In addition to the chronic irritative factor, cigarette smoking probably exerts an additional more active influence. Experimentally it has been demonstrated that tobacco can produce cancer, as evidenced by the researches of such men as Wacker and Schmincke, Leitch, Philippon, Lickint, Roffo, Morpurgo, and Boehncke." page 6, (4651)

(4772) Ochsner

"The apparent increase in the incidence of carcinoma of the lung stimulated much speculation concerning its cause. The numerous explanations advanced to account for this fact have been reviewed in previous publications. In the analysis of this series none of those factors was found to bear a significant relation to the occurrence of the disease. Both occupation and smoking, which have been particularly emphasized by some observers as possible etiologic factors, and which we were inclined previously to consider more seriously, were found to have no special significance in his analysis. Of the 147 patients in

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whom pulmonary resection was performed 76 per cent were smokers and 24 per cent were nonsmokers, and the number of those who had indoor occupations was almost equal to that of those who did outdoor work." page 322, (4772)

(4773) Ochsner, DeBakey & Dixon

"The numerous explanations advanced to account for the apparent increase in incidence in carcinoma of the lung have been reviewed in previous publications and will not be discussed here. In the 129 resected cases no factor was found which might bear a significant relationship to the occurrence of the disease. Neither occupation nor smoking habits, which some reports, including our own, have stressed as of possible etiologic significance, seemed of any special significance in this particular series (Charts 5 and 6: 75% smokers and 25% nonsmokers)." page 525, (4773)

(4867) Ochsner

"The cause of bronchogenic carcinoma is not known. There is some presumptive evidence that smoking might be a factor and might account for the increased incidence. It is conceivable that the long continued irritation of the bronchial mucosa caused by habitual smoking may be an etiologic factor." page 43, (4867)

(4871) Ochsner, DeBakey & Richman

"The etiology of bronchogenic carcinoma is unknown, aside from the fact that males are much more frequently involved than females, which permits the conclusion that there is a greater predisposition in the male. On the other hand one cannot say what the cause is of the increasing incidence of this type of malignant process. Although we previously were of the opinion that the chronic irritation resulting from excessive cigarette smoking was a factor, this cannot be proved. However, the fact that there is a parallelism between the number of cigarettes sold in the United States and the increased incidence of bronchiogenic carcinoma is interesting." page 596, (4871)

The changing opinion on the role of cigarette smoking can be derived from references (4772) (4867) and (4871). Ochsner concluded that both occupation and smoking had "no special

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included in the following checklist of 35 articles.

(4046) Hammond; Detroit, MI; G466

"In the present series the male sex predominated, there being 32 men to 8 women, or a ratio of 4 to 1. This high male incidence may be explained perhaps on the basis of indulgence in tobacco. Roffo in 1936 produced definite experimental evidence that tobacco has carcinogenic properties and that the cancer which occurs in smokers in the tissues of the lips, oral cavity, tongue, respiratory tract and lungs may be traced to the excessive use of tobacco. He found that the distillation and combustion products of tobacco, especially the tar, when applied daily over a long time on rabbits' ears, led in 95 per cent of the animals to the production of papillomas, which after nine months had degenerated into squamous cell carcinomas. Furthermore, he determined that a heavy smoker who consumes, for example, three packages of cigarettes per day, deposits 400 Gm. of tar per year, or nearly 10 pounds in ten years, on the mucosa of the oral and the respiratory system. That the continuous irritation from such large amounts of tar deposits must necessarily have a carcinogenic effect also in the human body appears reasonable enough. It has been suggested, especially by Weller, that other irritative factors, such as chemical, mechanical, bacterial, thermal and radioactive agents, might play an etiologic role in the production of carcinoma of the lung, but the influence of these factors in the present series was less apparent. The only exceptions may be represented by the 2 cases, 1 of a man and 1 of a woman, in which bronchiectasis of over eight years' duration preceded the onset of the carcinoma." page 781, (4046)

Note: Although Hammond cited smoking references, he did not publish smoking habits of his own series of 40 lung cancer patients.

(4047) Hanks; Sanatorium, TX; G555

"The etiology of primary carcinoma must be considered as dependent upon the same conditions that produce carcinoma elsewhere in the body. In common with all cancer, many theories have been advanced to account for its origin. All authors agree on one point, however, and that is irritation of the bronchial mucous membrane. Influenza has been advanced as a causative factor in the formation of this malignant condition. The basis for this accusation probably is that influenza causes a change of the normal columnar epithelium to a stratified

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squamous epithelium which is more easily excited to hyperactivity and therefore malignancy. Poison gas, tar and use of tobacco have received their share of the blame for this disease due to the irritant properties they contain." page 2597, (4047)

(4049) Higgins; Richmond, VA; G555

"Closely linked with the possible role of tar is the evidence against tobacco. The recent sale of a cigarette holder which encloses a cigarette through which the smoke is filtered is a graphic demonstration of the amount of tar resin introduced into the bronchial passages in the course of a day. The incidence of smokers in some series is remarkably high although Vinson noted the fact that only seventy of 140 cases of carcinoma of the tracheobronchial tree, at the Mayo Clinic, were smokers. Tobacco smoke as a lung irritant may be considered at least a possible cause of pulmonary malignancy in susceptible individuals but not necessarily a major factor. In any event, all known etiologic agents have in common the one characteristic of producing pulmonary irritation and, since they are so diverse, the only conclusion possible is that such irritation is the real activating or causative factor in the disease. Simons asserts that the reduction of all the present known facts to one formula is a positive result of the work so far performed." page 363, (4049)

(4059) Macklin & Macklin; London, CAN; Z566

"Other agents, such as roentgen rays, tobacco smoke and motor exhaust fumes, have been suggested as possible causes. The suggestion that roentgen rays are a cause is almost absurd, for the probabilities are that only a small percentage of those in whom cancer of the lungs has developed ever had their chest under roentgen rays before they came for diagnosis of their cancer. Motor mechanics working in garages where there is an abundance of exhaust fumes are said to show no higher incidence of pulmonary cancer than the general population, and Campbell stated that exhaust gases from internal combustion engines do not increase pulmonary cancer in mice. Tobacco smoke might be one factor in the increase of pulmonary cancer. The habit is one which permits long-continued use application of the smoke to the bronchial mucosa; it is, or at least was, a habit more prevalent among men; there are two possible agents which might prove to be cancer producing, namely, heat and the derivatives of tobacco. There are those who point out

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that the increase in the consumption of tobacco parallels the increase in the incidence of pulmonary cancer. This may or may not have significance. If tobacco is a factor, it must be proved that derivatives of tobacco are carcinogenic or that the repeated application of heated smoke is conducive to cancer. McNally stated that the tar in cigarette smoke contains enough chemical irritants to account for the increase in cancer of the lung. Roffo found among a group of 5,000 cancerous women 42 who exhibited cancer in what he called the 'smoke stream' namely, the lips, tongue, jaws, larynx and pharynx. All of these women were heavy smokers. He found that the products of burnt tobacco produced carcinoma when painted on rabbit ears, and he feels that there are probably many aromatic substances in tobacco that are carcinogenic. His findings are suggestive. But the increase in cancer of the lung should be much greater among females than among males, since smoking has increased among women far more rapidly in the last two decades than it has among men. Data published by the Metropolitan Life Insurance Company show that the incidence is not greater among females. The rates among the industrial policyholders of 45 to 74 years of age show that in 1917 the rate for pulmonary cancer among females was 2.5 per hundred thousand. This rose to 8 per hundred thousand in 1938, an increase of 220 per cent. The rate for cancer of the lung in males rose in the same period from 3.2 to almost 23 per hundred thousand, an increase of more than 600 per cent. Their conclusion is that it appears doubtful that smoking is a factor in causing cancer of the lung.

Controlled observations over a longer period are necessary to settle this point. Investigators must not rest content with finding that a high percentage of patients with pulmonary cancer are tobacco smokers; they must find that the percentage of smokers in this group is significantly higher than that in the general population of a similar age and sex distribution.

When we review all the theories on the cause of pulmonary cancer, we find that not one supposed cause has been proved to be a real cause and that none of the alleged causes has been investigated with sufficient statistical accuracy to enable the observer to pass an opinion carrying any weight. No one cause, no sum of causes, no common factor in them, namely, chronic irritation through inflammation of the bronchial mucosa, has been demonstrated to occur with any greater frequency in patients with cancer of the lung than in a group from the general population of comparable age and sex distribution at a time sufficiently long before the

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onset of the cancer that it may be interpreted as antedating this rather than following it. Naturally, any condition which is a sequela of cancer of the lung may be found more frequently in patients with pulmonary cancer than in persons not affected with this type of cancer. Such a condition when obviously the result of cancer of the lung must be excluded from a discussion of the latter's causes." pages 944-945, (4059)

(4095) Tripoli & Holland; New Orleans, LA; G555

"The etiology of carcinoma of the lung is still not clear. The factors most frequently emphasized include dust, chemicals, gases, fumes and tobacco, as well as such pre-existing diseases as influenza, tuberculosis, and syphilis. The carcinogenic properties of silica and road dust, with and without tar, have been demonstrated in mice by Campbell, and their effects in humans seem to be supported by the reports of Schmorl and of Pirchan and Sikl. The widespread incidence of influenza, and the equally general use of tobacco, suggest a possible relationship, but the association is not clear, and neither these nor any other factors could be demonstrated as causal in any of the cases in our series." page 560, (4095)

(4096) Coleman; Columbia, SC; G550

"The increased incidence of cancer of the lung is both relative and real. The wider use of coal tar products exhaust gases from automobiles, tobacco smoking, and other agents resulting in chronic pulmonary irritation are considered to account for the real increase in cancer of the lung." page 46, (4096)

(4129) Bondurant; Jefferson Barracks, MO; G555

"Hammond cites Roffo who, in 1936, adduced what he thought was experimental evidence that tobacco is a possible cause of cancer, and that occurrence of malignant growths of the tongue, lungs, respiratory tract, lips, and oral cavity followed excessive smoking. Roffo reported that applications of the distillation and combustion products of tobacco, especially the tar, when applied daily for a considerable period of time over rabbits' ears, caused papillomas in 95 per cent of the animals; and that these, after 9 months, degenerated into squamous cell carcinomas. He also mentioned that a heavy smoker who consumes, for example, three packages of cigarettes per day, deposits 400 gm. or tar per

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year, or nearly 10 pounds in 10 years on the mucosa of the oral and respiratory tracts." page 388, (4129)

(4135) Diamond; Legion, TX; G988

"The nature of the patient's antecedent history offers the physician little aid in his efforts to establish the diagnosis. Some observers are of the opinion that chronic irritation is a major factor in the production of malignant changes in the walls of the bronchi. However, except for the unexplained high incidence of malignant pulmonary neoplasms among Schneeberg miners with pneumoconiosis, no definite evidence has been adduced in support of this concept. The actual existence of a significant relationship between the development of cancer of the lung and a previous history of smoking, prolonged exposure to irritating dusts or vapors, or the presence of long-standing bronchopulmonary infection has yet to be shown. Were smoking a factor of any moment, there should have been a marked change in the comparative sex incidence of the lesion in recent years, corresponding to the rapidly growing prevalence of the habit among women. Instead, the predilection of pulmonary carcinoma for men is as pronounced today as it was thirty years ago. ... Chronic bronchopulmonary irritation prior to the development of neoplasm was not particularly marked among our patients at Legion. Eleven of the men smoked; 8 were moderate smokers, 3 heavy smokers. In none of the cases did the patient's occupation or environment involve the continued inhalation of irritating substances. A history of previous respiratory affection was present in 8 patients: 5, all of whom smoked, had a chronic cough; 1 suffered from asthma; 2 had been through a siege of influenza during the epidemic of 1917. The absence of tuberculosis in these 20 patients with pulmonary carcinomata is noteworthy, for the hospital has an active tuberculosis service of more than 200 beds." pages 713-714, (4135)

(4143) Halpert; New Orleans, LA; G555

"The contribution of Dr. Menne and Dr. Anderson presents evidence that there is a relative as well as an absolute increase in carcinoma of the lung. Their data from the Pacific Northwest on necropsy material are almost identical with those reported by Rosahn from the East and with our own data from the South. Carcinoma of the lung, in fact, is becoming the second if not the first most common malignant neoplasm in the male.

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Chronic irritations from infections, inhalation of gases, foreign bodies and particularly smoking of tobacco with its nicotine and tar content may play a part, but perhaps more important is the fact that more people are reaching the cancer age. Whether the gross morphologic classification according to location and extent of the growth as suggested by Dr. Menne and the one by Dr. Karsner have any practical value remains to be seen. At present there are no gross criteria by which the cellular structure can be ascertained without microscopic examination." pages 2221-2222, (4143)

(4146) Hershberger; Seattle, WA; G555

"A review was made of the 16 proved cases seen at this hospital for possible etiological factors. These cases were white males, with the exception of one Negro. The ages on admission ranged from 44 to 70 years, the average age of all patients being 52.5 years. The occupations, according to the histories, were not significant and there was no evidence of exposure to unusual occupational hazards. Concerning their habits, 12 on admission gave a history of smoking, 5 using cigarettes. Ten men stated that they used some form of alcohol. A history of chronic pulmonary disease was obtained from 3 patients; one stated that he had a cough as long as he could remember; another stated that he had asthma and bronchitis for 15 years; the third had symptoms of pulmonary tuberculosis for nearly 5 years, and this diagnosis was made and proved by positive sputum examinations during his stay at this hospital. The Kahn test was positive in only 3 cases and negative in 13 in our own laboratory. That a positive serology can lead to confusion in the diagnosis of this condition is shown in a later paragraph." page 3, (4146)

(4148) Jackson & Jackson; Philadelphia, PA; K400

"From our record we can make the parallel statement that the proportion of smokers among patients with laryngeal cancer is very high. The researches of Roffo on the cancerigenic effects of tobacco are thorough; the results are interesting and important. This etiologic factor is important in relation to the study of incidence because in our experience the proportion of men with cancer of the larynx to women with this lesion is 10:1. Among our patients about 95 per cent of the men were smokers of tobacco; none of the women whose cases were recorded prior to two years ago was a smoker.

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Now that smoking among women is becoming deplorably common it will be interesting to note in the future the relative incidence in women. The same may be said of alcohol. Our observations lead us to believe that alcohol used in beverages is a cause of cancer of the larynx. This opinion is strongly supported by the results of investigations by research workers." page 59, (4148)

(4156) Menne & Anderson; Portland, OR; G466

"More recently investigators have turned their attention to the possible influence of the increased use of smoking tobacco (especially the marked increase in the use of cigarets). Myers pointed to the enormous increase in the number of cigarets consumed in this country. In 1880, 582,718,995 cigarets were consumed, in comparison with 169,847,245,964 in 1937. Myers noted also that the toxic products of the combustion and distillation of tobacco are carbon monoxide, ammonia, formaldehyde, methylamine, methane, methyl alcohol, hydrogen sulfide, pyridin, furfural, arsenic and hydrocyanic acid. Of these the nicotine and tar contents are thought to be the most harmful. The former is an irritant of mucous membranes and the latter is regarded as carcinogenic. Myers stated that 'the smoking habits unquestionably increase the liability to cancer of the mouth, throat, esophagus, the larynx and the lungs.' Cramer noted that habitual smoking producing chronic inflammation of the mouth, pharynx, larynx and bronchial mucosa was present among the steel workers studied by him. In comparing the influence of tobacco smoking with that of the gases coming from automobile exhausts, Cramer demonstrated that a 5 Gm. cigar yielded 200 mg. of tar (phenanthrene), while an eight hour drive 10 meters behind an automobile resulted in the collection of only 1.5 mg. of a similar tar. This author appeared to be convinced of the influence of tobacco smoking in the causation of bronchiogenic carcinoma. Roffo stated that 'the tobacco tars are very strong cancer producing agents and that they are in the 'same form as the coal tars and certain substances whose properties are very like those of the hydrocarbons distilled out of coal in their fluorescence and their spectrometry.' He produced cancers by the application of tobacco tars to the ears of rabbits. He pointed out that 'one can easily see large opportunity of cancerization in a regular smoker who consumes 1 kilogram of tobacco monthly, which means 70 cc. of tar.' In this manner Roffo reasoned that 'the average smoker loads in one year 840 cc. and in ten

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years over 8 liters of tar on his buccopharyngolaryngo-pulmonary membranes, which certainly have not the biologic resistance of the skin of a rabbit.' Turner and Willis observed bronchiogenic carcinoma in a gold miner who had influenza and smoked 1/2 pound (226 Gm.) of black tobacco a week.

Certainly the striking predominance of bronchiogenic carcinoma in men as compared with the incidence among women suggests either that in the industries men come in contact with an irritating substance or that the increased consumption (smoking) of tobacco by men as compared with its use by women is of great significance. It would seem that more careful recording of this histories to how much particular persons smoke would be of great value in determining the causal relation of the use of tobacco to bronchiogenic carcinoma. The average inquiry simply elicits information that the patient is or is not a user of tobacco. It is too early as yet to observe in the statistics of the literature the possible influence that tobacco smoking may exert on the incidence of bronchiogenic carcinoma in women who are now smoking cigarets, often more excessively than do men. A report by Rice, although it concerned a small number of patients (18 men and 12 women) seemed to indicate an increase among the women." pages 2218-2219, (4156)

(4233) Harrison; Shreveport, LA; Z666

"War gases have been mentioned but their importance seems to be slight. The same is true of tobacco smoke. It may be an irritant but it probably is not an important factor. If tobacco were the cause of lung cancer, why has not carcinoma of the lips and tongue increased at a rate parallel with carcinoma of the lung?" pages 2781-2783, (4233)

(4253) Perrone & Levinsen; Pittsburgh, PA; G955

"The etiological factor here as in other carcinomas is still a mystery. The various factors suggested are heredity, trauma, pulmonary tuberculosis, influenza, pneumoconiosis, chronic pulmonary diseases, roentgen-ray, dust inhalation, tin particles, motor exhaust fumes, war gases, occupational hazards, tobacco smoking. Simons concluded that no single etiologic agent could be pointed out as the cause of pulmonary cancer. He states, 'In any event, all known etiologic agents have in common the one characteristic of producing pulmonary irritation and, since they are so diverse, the only

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conclusion possible is that such irritation is the real activating or causative factor in the disease. This is not to say, of course, that all chronic pulmonary irritations ensue in carcinomas; and it is to be hoped that future research will make this definition of the cause either more specific or more conclusive or both." pages 13-14, (4253)

(4334) Grace; Brooklyn, NY; G205

"After having had an opportunity to observe, over a period of ten years, an unusually large series of patients with cancer of the lung, in two of the large municipal hospitals in New York City, two very distinct elements were noted in these patients: First, they were always men; second, they were heavy cigarette smokers and almost always inhalers. It is obvious, therefore, that this product of combustion deeply inhaled into the lungs of cigarette smokers - for cigarette smokers usually inhale - is deposited in the lung along the entire bronchial system, and most of the biologic principles are present, I believe, to produce bronchogenic carcinoma in accordance with well known animal experiments." (page 361, Harris SOA quotations in Table 2)

"There is no experimental proof at hand to demonstrate that the smoking of many cigarettes was the cause of lung cancer, however, some aspects of this problem should be carefully evaluated." page 361, (4334) omitted by Harris.

(4353) Murray; Brooklyn, NY; G666

"Aside from the knowledge that some form of chronic irritation plays a leading role in the etiology of these tumors nothing really definite is known. Much speculation has been indulged in but nothing actually proven. Simons reviewed exhaustively all possible etiological factors, pointing out that some form of chronic irritation underlay practically all of them. With slight rearrangement these etiological factors are as follows:

- 1) Chemical - Inhalation of (a) tar particles, (b) motor exhaust fumes, (c) war gases, (d) tobacco smoke, (e) certain dusts (as in pneumoconiosis or in the case of the Schneeberg miners). It is assumed that there has been a marked increase in the above during the past 30 years, coincident with the increase in the incidence of bronchogenic carcinoma.

- 2) Mechanical - Trauma (19 out of 500 cases).

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3) Bacterial - (a) Tuberculosis 15 per cent, (b) influenza (again the increased incidence since the great influenza pandemic of 1918-1919 has been noted), (c) chronic respiratory infections and their sequelae - lung abscess, chronic bronchitis, bronchiectasis (many believe the latter the result rather than the cause).

4) Heredity - 64 out of 930 cases.

All the above may be vital contributing factors but none of them by themselves have been proven conclusively to have produced cancer of the lung. Apparently some constitutional defect, probably congenital, must be present to pave the way for the deleterious effects of chronic irritation." pages 390-392, (4353)

(4364) Wallace & Jackson; Galveston, TX; G177

"We believe that tobacco smoking plays a definite role in the causation of primary lung carcinoma. ... In connection with tobacco smoke we should like to point out the increase in incidence of bronchogenic carcinoma in women in the past several decades and the relationship of this to the increased incidence of smoking in women during this period." page 607, Harris' SOA quotation]

"As in all cancer, there is no known definite cause for carcinoma of the bronchus. Heredity has often been mentioned." page 606, (4364) omitted by Harris. Also, note that twelve of 28 patients had no information on smoking habits.

(4425) Clagett & Brindley; Chicago, IL; G555

"The opinion frequently has been expressed that the increase in bronchogenic carcinoma may be due to the increase in smoking and the inhalation of smoke. Nicotine, pyridine bases, phenol bases, ammonia and certain added hygroscopic agents all have been shown to act as irritants to the bronchial mucosa. Pulmonary carcinoma has been produced in experimental animals by the tar from cigarette smoke. Ochsner and DeBaKey concluded: 'It is our definite conviction that the increase in the incidence of pulmonary carcinoma is due largely to the increase in smoking, particularly cigarette smoking, which is universally associated with inhalation.'" page 840, (4425)

(4440) Grace; New York, NY; G205

"Using the numerous investigations (by Roffo and others) reported in the preceding pages as a springboard

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from which to make further conjectures on the relationship between tobacco poisoning and certain clinical entities which are generally associated with a heavy smoking habit, we may differentiate two such groups: 1. cancer of the lip and oral cavity, and 2. cancer of the lung. The former is most frequently encountered in pipe and cigar smokers who rarely inhale, but in whom the irritating substance of tobacco is deposited on the lips and tongue. In cancer of the lung, often occurring in cigarette smokers, this toxic irritant is deposited in the bronchi during the process of inhaling smoke. There appears to be no doubt whatsoever that, in the heavy smoker, tar, with its chemical byproducts, enters the etiological picture in the development of neoplasms." page 328, Harris' selected quotation of (4440)

(4477) Tinney; Rochester, MN; G500

"Unfortunately, bronchiogenic carcinoma does not have characteristic symptoms. The symptoms are the same as those produced by any pulmonary inflammatory disease and depend essentially on the size and location of the tumor. Cough was an early symptom in 81 per cent of the cases in this series. The cough was usually dry and nonproductive at onset and did not differ from the so-called cigarette cough, that is so indigenous in the general population. The cough does not become productive of a purulent sputum until the size of the tumor is sufficient to obstruct the bronchial lumen and cause retention of secretions in the distal bronchi. When the retained secretions become secondarily infected, attacks of chills and fever develop that are usually relieved in a few days by drainage of the secretions. Such episodes occurred in approximately half of the cases which I studied and the diagnosis of pneumonia was frequently made." page 355, (4477)

(4533) Holinger, Hara & Hirsch; Chicago, IL; G555

"The inhalation of tobacco in smoking is considered by some as a factor causing cancer. It is generally known that cancer among smokers is much more prevalent in the so-called smoke tract - the lips, mouth, larynx and bronchi - than in nonsmokers. Ninety per cent of a large series of patients observed at the Cook County Hospital were smokers. Fifty of our own patients were heavy smokers. However, 14 stated that they did not smoke, and there is no mention of this habit in the remainder of the histories." page 7, (4533)

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(4554) Muller & Miller; Philadelphia, PA; G566

"Inhalation of light oil derivatives of coal tar and dusts containing silica have likewise been shown to be of etiologic significance in lung cancer. The high incidence of lung cancer in the male sex as compared to that of the female sex has been attributed to the use of nicotine, but the recent increase in female smokers has not led to an increase in lung cancer in females." page 42, (4554)

(4560) Potter & Tully; Boston, MA; K500

"43 male lung cancer clinic patients, aged over 40 years, compared to 1,847 male clinic patients with diagnoses other than cancer. 30.2% heavy smokers and 7.0% nonsmokers among lung cancer cases. 23.0% heavy smokers and 26.0% nonsmokers among controls." (Harris' paraphrased results; figures do not appear in the cited article)

"Information on the use of tobacco was obtained from 2,927 male clinic patients over the age of 40. They were divided into those who used no tobacco, those who reported slight use, moderate use, and excessive use. Attack rates were computed for cancer of the buccal cavity, digestive tract, respiratory tract, skin, and for cancer of all other sites. There was a definite association between cancer of the buccal cavity and the use of tobacco. There also appeared to be some association between the use of tobacco and cancer of the respiratory tract. These findings confirm the opinion held by many clinicians." page 488, (4560)

(4615) Clerf & Herbut; Philadelphia, PA; G455

"Many writers believe that inhalation of tobacco smoke is a responsible factor. Since chronic irritation is generally accepted as a predisposing cause, there should be ample evidence to support the theory that inhalation of tobacco smoke, particularly from cigarettes, is a factor. This habit is practically universal and a majority of patients with carcinoma of the bronchus smoke either moderately or excessively. Irrespective of its being an etiological factor, smoking more than anything else contributes to delay in diagnosis by making a common, early and important symptom, namely, cough." page 169, (4615)

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(4635) Horn; Baltimore, MD; G466

"The use of tobacco and its relation to lung cancer has been a favorite subject of investigation. Ochsner strongly affirms that the rise in bronchogenic carcinoma is caused by the increasing use of tobacco. Campbell in a statistical study found those engaged in the preparation and sale of tobacco to have an abnormal liability to lung cancer. Grace suggested that 'possibly the carcinogenic irritants from tobacco tar are deposited in the lung and the end result of this irritation in a biologically susceptible individual is the production of bronchogenic carcinoma.' No one proposes an explanation, however, to interpret the fact that while by far the greatest increase in smokers during the past two decades has been among women, bronchogenic carcinoma has been seen strikingly more often in males than females. In the University of Maryland Hospital series, forty cases occurred in men and five cases in women." pages 170-171, (4635).

Note: There is no information on smoking habits of 45 reported cases, in spite of author's awareness of the literature.

(4718) Berg, Poppe & Havlicek; Portland, OR; G555

"Since the question of use of tobacco appears on the routine history form at the Veterans Hospital, an unusually good record of this was obtained. In the entire series there were only four nonsmokers, and many of the patients were noted to be heavy smokers. The question of the relationship of cigarette smoking to the etiology of bronchogenic carcinoma has been an interesting one and has been discussed by many authors. Since approximately 90 per cent of male patients smoke, no conclusions can be drawn from this fact alone." page 452, (4718)

(4754) Humphreys; New York, NY; G500

"The outlook for a patient who develops carcinoma of the lung is so miserable that many doctors consider it completely hopeless. Because until recently primary carcinoma has been thought to be a rare disease, the possibility of its presence is too often overlooked by the general practitioner. Only after a protracted period of waiting for a turn for the better which fails to occur is he forced to realize that he is dealing with something more than an inflammatory process. Too often, even when the possibility is considered, there is

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a tendency to procrastinate, in the conviction that, if a tumor is present, the patient is in any case doomed. This tendency is increased by the fact that these lesions frequently occur in heavy smokers whose early symptoms are masked by a long history of cough, and whose illness apparently begins with symptoms of acute infection, symptoms which respond deceptively well to sulfonamide or penicillin treatment. The discomfort of bronchoscopy is a small thing to ask of a patient who is faced with possibility of death from this disease, yet it is surprising how often the chance it affords of establishing the diagnosis early is withheld." page 3330, (4754)

(4819) Bradshaw; Winston-Salem, NC; G900

"Lung cancer occurs predominantly in patients over 40, but is occasionally seen in teen-age youngsters. For some unknown reason males are afflicted five or six times as frequently as females. This fact has been used by some as an argument that smoking has an irritating effect which is a factor in the production of lung cancer. Such reasoning has no foundation on either experimental or clinical evidence. The incidence of cancer in patients with truly irritating diseases of the bronchial tube, such as bronchiectasis, has never been shown to be greater than in normal individuals. Many patients, both male and female, who have lung cancers have never smoked." page 187, (4819)

(4822) Churchill; Boston, MA; G905

"Nothing is known about the cause of the disease that can be translated into effective preventive measures. It is possible that an actual increase in the incidence of pulmonary cancer has taken place during the first half of this century. Several statistical studies support such an interpretation. On the other hand, Boyd, who is in a position to speak freely of the shortcomings of pathologists, thinks the disease was not recognized twenty years ago because it was not looked for. At any rate, evidence that pulmonary cancer was on the increase led to several speculations about causative agents, and among other things, cigarette smoking was incriminated. Further knowledge about the nature and the mode of action of carcinogenic agents, and a careful recording of the smoking habits of ample number of patients with the disease, provide no factual evidence on which advice to give up smoking for this reason can be based. Exposure to radioactive ores has

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been correlated with a high incidence of the disease in classical studies on European mine workers. It may be well to bear this in mind." page 456, (4822)

(4847) Levitt; Detroit, MI; G566

"Many investigators have endeavored to establish a connection between bronchogenic carcinoma and chronic irritation of the respiratory tract. Tobacco smoke, air pollution from the exhaust of automobiles, dust raised from tarry roads, have all been suggested as possible causes, but as yet, none of these factors has proven to be the specific cause." page 396, (4847)

(4858) Madore; Montreal, CAN; G655

"Opinions vary greatly on this point. The high incidence of cancer in males as compared with females has been attributed to the use of nicotine, but the recent increase in female smokers has not led to an increase in lung cancer in females." page 146, (4858) from Alwens & Jones, 1936, ref. 5.

(4859) Martin; New York, NY; Z600

"The pre-existence of chronic local irritation which may so often be shown to play a part in the causation of malignant growths of the oral cavity is not readily demonstrated in cancer of the larynx. Although excessive smoking with inhaling, voice strain and syphilis are undoubtedly etiologic factors in an occasional case, these forms of irritation cannot be shown to have a significant etiologic role in most cases of laryngeal cancer. The disease usually appears to arise spontaneously. Leukoplakia of the larynx (pachydermia larynges) sometimes undergoes malignant transformation." page 1366, (4859)

(4876) Quick & Brindley; Galveston, TX; G455

"Speculation concerning predisposing causes has been rife. Street dust, stone dust, exhaust from automobile fumes, and tobacco smoke have all been blamed. It is of interest that the curve of incidence of bronchiogenic carcinoma parallels the rising curve of cigarette sales. We should watch the incidence of carcinoma of the lung in women in view of the recent general trends in smoking." page 627, (4876)

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(4866) O'Keefe; Philadelphia, PA; G566

"Holinger and his associates reviewed the secondary etiologic factors in a recent paper. In their analysis of such inhalation irritants as coal dust, silica, exhaust gases, road tar and tobacco smoke, they concluded that 'without further corroborative evidence, (these) too, must be considered coincidental.' Clerf and Herbut placed a unique and pertinent interpretation on the relationship of tobacco smoke: 'Irrespective of its being an etiological factor, smoking, more than anything else, contributes to delay in diagnosis by masking a common, early and important symptom: namely, cough.'" pages 347-348, (4866). Note: There was no information on the smoking habits of 131 patients reported in the article even though O'Keefe was aware of literature implicating cigarette smoking.

(4938) Hayes; Saranac Lake, NY; G555

"These are unknown, although excessive smoking of tobacco and, in certain industries, radioactive emanations have been blamed. The increase incidence has been parallel in the last four decades to industrial development with its noxious chemicals and gases." page 895, (4938)

Incidence of cigarette smoking. It was the opinion of most American clinicians cited above that cigarette smoking incidence among lung cancer patients was not higher than that in the general population. Among 35 articles, there were four that favored causal hypothesis of cigarette smoking (4334) (4364) (4440) (4560). Each one was cited by Harris in his Table 2. Two other articles were used by Harris in his SOA Report (4156) (4759), but the remaining 28 were overlooked. The following overlooked articles contained a review of the literature implicating smoking as a cause of lung cancer: yet smoking habits of patients reported by the author were not mentioned (4046) (4718) (4866).

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### Smoking Habits Among Europeans

The earliest articles suggesting a causal relationship between lung cancer and cigarette smoking appeared in German medical journals and were later followed in English. It was probably more than a coincidence that early literature on cigarette smoking and lung cancer was published in German. There was a suggestion that Nazi medicine was against the use of tobacco that was manufactured and sold by Jews. An anti-tobacco organization flourished during the war.

Germany and Austria. The first suggestion of a causal link was made in 1929 by Lickint, based on a coincidental rise in incidence of lung cancer and in cigarette smokers. The first reported comparison of smoking prevalence in lung cancer patients and controls was reported in 1939 by Muller. During World War II, Schairer & Schoeniger confirmed Muller's conclusions that smoking prevalence was more frequent among lung cancer patients compared to a group of control among males in Germany. For completeness of this review devoted to the 1940's, the following publications in German since 1929 are included (see also Chapter III, page 218).

(2931) Lickint

"Review of laboratory and clinical evidence on tobacco and cancer. Rise in cigarette use linked to rise in lung cancer." (quoted by Harris)

(3031) Mertens

"Increased incidence of lung cancer linked to tobacco. Shift in cancer from oral sites to lower

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respiratory tract linked to shift from pipes and cigars to inhaled cigarettes." (quoted by Harris)

(3572) Lickint

(Not quoted by Harris; needs English translation)

(3985) Muller

"Comparison of 86 male lung cancer decedents with 86 healthy men of the same age. 65.1% heavy smokers and 3.5% nonsmokers among the lung cancer cases. 36.0% heavy smokers and 16.3% nonsmokers among the control cases." (quoted by Harris; Muller discussed role of occupation; no further publications by Muller)

(4311) Schairer & Schoeniger

"Comparison of 93 male lung cancer decedents autopsied (average 53.9 years) with 270 men aged 53 and 54. 31.2% heavy smokers and 3.2% nonsmokers among lung cancer cases. 9.3% heavy smokers and 15.9% nonsmokers among controls." (quoted by Harris; no further publications after appearance of (4311))

(4893) Wassinck

"134 male clinic patients with lung cancer compared to 100 normal men of same age groups as cases. 54.8% heavy smokers and 4.8% nonsmokers in lung cancer group. 19.2% heavy smokers and 19.2% nonsmokers in the control group." (quoted by Harris; patients were from Amsterdam)

I am in the midst of collecting articles by each of the six German authors listed above. A recent trip to East Germany failed in finding additional information on the *Scientific Institute for Research on the Danger of Tobacco*, and the *Institute of Pathology, Friedrich Schiller University* in Jena. These were the affiliations of Schairer & Schoeniger when they submitted the results of a retrospective study of lung cancer patients and control subjects (4311). There were no subsequent

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publications by Mertens, Muller, Schairer & Schoeniger and Wassinck during the late 1940's and 1950's. Only Lickint continued to publish on smoking and health through the 1950's and 1960's (See Chapter V). Muller wrote his comparative study of lung cancer patients with controls without lung cancer as a thesis and did not publish on any other medical topics.

Great Britain and Switzerland. The Science Citation Index affords an opportunity to determine whether the suggestions by German writers were accepted or denied by other Europeans. Until the analysis of citations is complete, there are a few articles compiled from Index Medicus:

(4267) Wegelin; Berne, SWI; G555

"The effect of smoking may be similar now that Schurch and Winterstein, as well as Roffo have induced skin cancer by the use of tobacco tar. Some authors, such as Lickint, Arkin and Wagner, Fleckseder, Schrek, Thys and F. H. Muller emphasized the harmfulness of smoking, particularly the inhalation of cigarette smoke, and Muller found 56 heavy to extremely heavy smokers and only three nonsmokers among 86 men with lung cancer. The remarkable preference for the male sex is accounted for by this factor, but it must be noted that despite the increase in smoking among women, there is not yet any shift in the sex ratio. Although Mertens obtained epithelial metaplasia of the trachea and bronchi and degeneration of the mucosa with purulence in mice exposed for a long time to the inhalation of tobacco smoke, he did not obtain lung cancer, and the etiologic relevance of smoking to the induction of lung cancer is not yet established." page 38 of English translation, (4267)

(4336) Harnett; London, GBR; G506

"The percentage of smokers was estimated in a group of 69 men and 18 women, mostly from one hospital. Of the men 4.3 per cent. were non-smokers, 26.1 per cent. moderate, and 40.5 per cent. excessive smokers (over 3

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oz. of tobacco per week) with 29 per cent. not stated. Of the women, one-third were non-smokers, one-third not stated, and the remaining third were moderate smokers." page 36, (4336)

(4933) Fulton; London, GBR; G460

"No attempt has been made in this group to analyze the cases in terms of the possible effect of tobacco. Case histories, unless designed in such a way as to cover this point in specific terms, do not provide information of sufficient accuracy and consistency to use as a basis for analysis. It would not be surprising to find that tobacco was an etiological factor and, despite the fact that smoking is by no means confined to the male sex, it may have some bearing on the differing sex incidence. It may, for example, be important to determine whether the subject habitually inhales cigarette smoke, or whether it is merely puffed in the mouth. My impression is that most women smokers do not habitually inhale, while most men do.

The possible relationship between tobacco and carcinoma of the lung is being specially investigated by Dr. A. Thelwall Jones in Liverpool, and while the results of his investigation have not so far proved conclusive, the evidence to date points to tobacco as an etiological factor of possible statistical significance." page 778, (4933)

(4950) Mason; Newcastle-upon-Tyne, GBR; G650

"Perry of the London Hospital, has found that industrial exposure to arsenic and certain other metallic substances may probably be associated with the aetiology of lung cancer; but such industries are not, so far as I know, represented in our area. Perry has also remarked that arsenic is present in carcinogenetically significant quantities in cigarettes; but this is difficult to reconcile with the disproportionate sex-incidence despite the vast increase of smoking among women, especially since married women appear to be more commonly affected than their single sisters." page 587, (4950)

The above list will be expanded after completion of searching the Science Citation Cumulative Index for 1945-1954 (see Chapter V).

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Questionable Applicability of German Studies to Americans

The most important reason in questioning the applicability of German studies to the United States is that the incidence of smoking habit among Germans did not necessarily apply to Americans during the 1940's. In a 1935 Fortune magazine poll, the incidence of smoking was 53% of adult men and 18% of adult women (3541). The survey noted that incidence of smoking for men and women was higher among urban populations.

During 1939 and 1940, Ley and his collaborators questioned life insurance extension examinees regarding their smoking and drinking habits. The responses were confidential so that the examinees had no reason to withhold information with respect to their habits. The conclusions relating to smoking habits are in a highlight publication written by Short, Johnson & Ley from the Life Extension Examiners, New York (3982).

"In an attempt to learn what, if any, symptoms are produced in comparatively healthy ambulatory individuals by the use of tobacco, an unselected group of insurance policy holders were asked to fill out a questionnaire at the time of their periodic health examination. The questionnaire was designed to elicit their practices with reference to the use of tobacco, but contained no reference to physical signs or symptoms. This latter information was obtained independently from the physical examination and medical history which were recorded separately. Thus, by separating the time and method of obtaining the two kinds of information, it was hoped to avoid suggestion and bias. Of 2,031 cases studied, 1,292, or 63.7 per cent, habitually used tobacco; 496, or 24.4 per cent, were nonusers; 104, or 5.1 per cent, used it only occasionally; and 139, or 6.8 per cent were former users who had discontinued the practice. ... The complaints recorded are of especial significance because they were entirely spontaneous, written by the examinee

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on a history form, and not elicited by questioning. It should be emphasized that both groups were treated exactly alike and the findings therefore cannot be biased. We believe that the findings in this study indicate a trend in accordance with the recent report of Pearl, who found mortality markedly increased among heavy smokers. It is hoped that further studies will demonstrate more definitely the manner in which tobacco exerts its influence and the chief hazards attached to its usage." pages 587-589, (3982)

In 1940 Ley reported the incidence of smoking and drinking among examinees for life insurance extension (4099). The responses were confidential so that the examinees had no reason to withhold information with respect to their habits. The conclusions derived from 10,000 examinees were as follows:

"The incidence of both smoking and drinking among males is fairly constant after the age group 20-29. In all age groups the male incidence for smoking is higher than for drinking. The frequency of both smoking and drinking among females reaches a peak in the decade 20-29 after which point both practices decline through life. Unlike the experience for males, the female incidence of drinking is higher at every age period than that of smoking, with a slight exception for the youngest age group.

The practice of smoking among males is higher in the New York metropolitan area than in the rest of the country up to the age group 40-49. After that point the New York incidence is lower. The habit of drinking among females is higher at each age group for those in the New York area.

Approximately 64 per cent of males and 21 per cent of females over 10 years of age in the United States use tobacco. Approximately 57 per cent of males and 29 per cent of females use alcohol. Approximately 7 per cent more men smoke than drink, yet 8 per cent more women drink than smoke. Of the total figures, regardless of sex, approximately 43 per cent of the population use tobacco and 44 per cent use alcohol." page 63, (4099)

The geographic distribution of examinees was not mentioned by Ley, other than differentiating the New York metropolitan area

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from the rest of the country. There was no discussion of health differences associated with smoking and drinking.

A questionnaire sent by Schwartz (4568) to about 50 sanatorium directors contained the following questions:

- "1. Do you think smoking is harmful to tuberculosis patients?
2. Do you discourage your patients from smoking?
3. What rules, if any, do you set up toward control of smoking?
4. What arguments do you employ to discourage the habit among your patients?

The responses were summarized by Schwartz from Pine Crest Sanatorium, New York, as follows:

"A questionnaire was sent to about fifty sanatorium directors to obtain their opinion concerning smoking. Only 2 per cent felt that it was not harmful, but only 16 per cent had rules which rigidly forbade the practice. Most of the men permitted smoking in certain cases or ignored the fact that the rules were being broken. This attitude is engendered by the fact that it is quite difficult to discourage patients from a habit of long standing in return for a benefit which is of questionable value. An examination of the more recent literature leads to the conclusion that since smoking is harmful even to normal people it is bound to have a deleterious effect upon the respiratory tract of individuals who are suffering from tuberculosis. It is felt that the best approach to the problem would be a definite rule forbidding smoking with frequent explanations about the dangers inherent in the practice." page 1542, (4568)

Schwartz used 22 references in his discussion of health effects of smoking. There was no mention of any German author; Roffo was mentioned as quoted by an American author. The following references appeared in Schwartz's list of references, as well as in Harris' SOA report: Bogen, Hoffman, and Proetz. However, it should be noted that the question was specific for tubercular

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patients. The responses among the directors were as follows: 72% that smoking was harmful in excess; 2%, not harmful; 26% definitely harmful.

Macklin wrote three articles criticizing the literature on increase in lung cancer which she interpreted as unproven during the 1940's. The articles (4059) (4244) (4857) are highly recommended for detailed reading because pitfalls in dealing with cancer statistics could be applied to publications not only for the 1940's but also through 1966 (Part Three). Macklin's most important conclusions were items 5 to 8 as follows"

"5. The question we wish to determine is not whether lung cancer, meaning by that diagnosed lung cancer, is increasing in hospital cases, but is diagnosed lung cancer increasing in the population of the age and sex distribution which is capable of showing it? Therefore, the only way of determining this point is to study the incidence of diagnosed lung cancer in the population at large, and not in the small fragment of the population which comes to autopsy. Therefore, data from all hospitals within a state for two periods chosen so that the age and sex distribution of the population of the state is known, thus preferably in a census year, should be added together and analyzed. Cities are not large enough in their scope, since they draw obscure cases from surrounding rural areas in different proportions in various years. Each state, however, has usually centers that are apt to draw patients from within their own borders.

6. It will probably be found that diagnosed lung cancer is increasing both relatively and absolutely, but the increase will probably be much smaller by this method than by the ones adopted by most workers, in which age and sex distribution of the lung cancer cases and of the standard group were ignored. Lung cancer will be increasing because it is being diagnosed in more cases in which it exists than was formerly the case, and will be increasing no doubt because persons of lung cancer age are having fewer diseases to die of today than they had before, and hence must die in ever increasing numbers of the ones which remain.

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7. The data which are used to support the idea that lung cancer has increased faster than other forms of cancer cannot be used to support that conclusion, since we do not know what proportion of lung cancer cases were unrecognized formerly and what proportion are unidentified today. We can merely state that diagnosed lung cancer is increasing at a rate which appears to be faster than that of other diagnosed cancers.

8. The search for environmental factors supposed to be the basis of the unduly great increase in lung cancer should await further proof that the increase in diagnosed cases has been as spectacular as it has been claimed to be." page 324, (4857)

#### Experimental Carcinogenesis

The animal studies reported during the 1940's were mostly reported by Roffo on "tobacco tar" applied to rabbit ear. I have obtained additional references by Schurch, who reported results contrary to those reported by Roffo in the 1930's (See also page 243 and (3570) (3571) (3987)). The skin painting studies in mice and rats were either negative or showed less activity compared to topical effects of coal tar. There were two mouse inhalation studies that were negative in results.

Roffo's rabbit experiment and other studies. The experiments on "tobacco tar" conducted by Roffo during the 1930's were extended through the 1940's (see Chapter III, pages 236-244). The contents of articles that were omitted in Chapter III, 1930's, and those published during the 1940's, can be summarized as follows:

(a) Oral leukoplakia (3035) and gastric cancer (3126) (4112) (4211) (4214);

(b) Carcinogenic effects on rabbit ear from repeated administration of tobacco tar (4011) (4012) (4013) (4014) (4018) (4111) (4113) (4116) (4212) (4213) (4312) (4313) (4315) (4316);

(c) Detection of benzopyrene in tobacco tar by spectrometer and fluorescence (3942) (3948) (4017);

(d) Carbon monoxide in blood of cigarette smokers and potential cardiovascular effects, co-authored with Roffo, Jr. (3247) (3883) (4016) (4114);

(e) Exchange of correspondence between Roffo and Florey from Chicago (4275) (4276) and publication of Florey's article in Spanish (4274);

(f) Distribution of anti-smoking leaflets and publication of anti-smoking activities in 1942 issues of Boletin del Instituto de Medicina Experimental (4276) ; and

(g) High incidence of oral and lung cancer among cigarette smokers (4215) (4314) (4317) (4333).

Latin American and North American reaction to Roffo's publications. The scientific validity of Roffo's rabbit experiments were criticized because of manner of extraction of "tobacco tar." An excessively high temperature was used characterized as a process of "destructive distillation." Jaffe, Jaffe & Potenza, from Caracas, Venezuela, expressed this criticism in a Spanish article that needs translation. Their brief four-paged report (4640) was a theoretical criticism based on rat experiments and was overshadowed by over a thousand pages of Roffo's results on

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"tobacco tar" in rabbit experiments. Two Latin American publications acknowledged the reports of Roffo without offering any confirmation (4203) (4467), but other Latin Americans appeared to have ignored his publications (4034) (4074) (4320) (4521).

Roffo's scientific publications were included in an anti-smoking article entitled *Universal Toxicomania of Tobacco* (4115). The posters are English translations of Roffo's Spanish anti-smoking leaflets distributed in his Institute's "Boletino" (4276). In 1943, several authorities from Europe contributed to a *Libro de Oro* which included Hartmann (4048), Wassink (4893), and others that will be ascertained as soon as I obtain a copy from Buenos Aires.

Conflicting results among Roffo, Flory and Sugiura in rabbit experiments. Roffo reenforced his rabbit ear painting experiments by injecting tobacco tar directly into the lung parenchyma (see Chapter III, page 238). Roffo published a summary in English:

"This process is characterized by the production of 4 little tumours in the left lung lobe (site of injection), presenting all of them the structure of squamous carcinomata with horny globules. I consider this result as a contribution of value to the explanation of the abundant lung cancerization in men. Although it could be reasonably objected that the repeated injection of a drop of tobacco tar does not correspond with what is going on in ordinary human life and that such a brutal action is bound to produce a trauma, we nevertheless wanted to point out, once more, the carcinogenic function of this product, either injected in the lung, or in other tissues. As for discarding the objection of the energetic action of the injection which might be considered as a coadjuvant cause in the development of this process, we but need to remind the cancerization

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obtained by us in rabbits, by a superficial painting of their ears' skin with tar, each 2-3 days, without any other factor interfering." page 115, (4313)

Flory, a pathologist from the University of Chicago, repeated Roffo's ear painting experiments with the following results:

"Twelve rabbits were painted on the ears with a tar produced by the destructive distillation of tobacco at from 350-700°C. Between the 49th and 79th day all rabbits developed tumors at the painting site. The rabbits lived from 238 to over 600 days. Sixty-eight of the tumors examined histologically were papillomas, and 5 were carcinomatoid tumors. No carcinomas were produced. A 130-150°C. destructive distillate tar produced tumors in 16 out of 17 rabbits, but more slowly than the 350-700°C. tar. Forty of these tumors were papillomas and 5 carcinomatoid tumors.

Twenty-four rabbits were painted with tar obtained by smoking tobacco in pipes. Tumors were produced in from 37 to 374 days in 22 out of the 24 rabbits. Seven animals have lived over 640 days. Thirty-six tumors examined histologically were papillomas and 2 were carcinomatoid tumors. No carcinomas were produced.

What then is the status of these carcinomatoid tumors? In this work with tobacco tars evidence does not indicate what the ultimate fate of these tumors would have been. Most of the tumors were identified only at autopsy, although some were seen very early in the painting period. It is of importance to note the absence of definite metastases in all 11 animals with carcinomatoid tumors. It was not proved that such tumors could produce distant metastases. In view of the work of Rous and Kidd it would seem likely that the invasive behavior of these tumors depended on the repeated application of an extrinsic stimulus rather than on an intrinsic capacity for unrestricted growth. There is no evidence that the production of these carcinomatoid tumors in rabbits is an indication of carcinogenic activity of the tobacco tars." page 274, (4037)

Although Flory specifically denied carcinogenic activity, Roffo interpreted the negative result in the opposite way (4276), as did Harris in his SOA report.

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Sugiura from the Memorial Hospital, New York City, painted rabbit ears with combustion products of tobacco distilled between 100 to 900°C. (4091). Sugiura's article is a highlight publication with results that conflicted with those of Roffo:

"Our results with rabbits are not in conformity with the findings of Roffo, who succeeded in producing a large number of papillomas and true malignant growths after continued application of tobacco tar. Since Roffo's results seem undoubtedly significant, it is possible that some other factor than tobacco is responsible for the discrepancy. Roffo subjected tobacco of various kinds to fractional combustion distillation in a stainless steel retort, whereas we used an iron retort. It is difficult to believe that any hydrocarbons with a phenanthrene nucleus, which Roffo claims are contained in his combustion products of tobacco, should break up by our method of distillation. In addition, Kennaway has shown that the carcinogenic substance of coal tar is not found in any appreciable quantity below 550°C.

Little information is available concerning the presence in tobacco tar of carcinogenic hydrocarbons identical with those contained in coal tar. In 1932, Cooper, Lamb, Sanders and Hirst subjected tobacco tar products to spectrographic analysis to disclose a possible carcinogenic agent but reported inconclusive results. It was said, however, that all the samples of tar, whether obtained at low or high temperature, exhibited fluorescence. Schurch and Winterstein, in 1935, reported that the fractions obtained from tobacco tar did not contain polycyclic aromatic hydrocarbons related to the carcinogenic hydrocarbons contained in coal tar. Recently Roffo made intensive spectrographic examinations of products of combustion of tobacco and found hydrocarbons with a phenanthrene nucleus identical with that in the carcinogenic hydrocarbons present in coal tar. Roffo, however, made all his spectrographic analyses with impure complex mixtures. No definite conclusions can be drawn from the absorption bands of these bodies until the specific hydrocarbon is isolated in pure chemical form." page 48, (4091)

The subject of analysis for polycyclic aromatic amines is discussed below (*Occupational Exposure to Coal Tar*).

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Suguiura's negative results in rat ear. Sugiura noted that although rat skin was extremely resistant to the carcinogenic action of coal tar and hydrocarbons, it was highly susceptible to the cancer-producing effects of ultraviolet rays (4091). Sugiura cited Roffo and Beard who obtained positive results derived from rat ear painting experiments. However, Sugiura obtained negative results using tobacco tar:

"A series of experiments was conducted to determine whether the ears of rats share the exemption from the carcinogenic action of tobacco tar that is shown by the skin of mice. The internal surface of the ears was painted with the combined dark brown oily liquids of the first and second distillates, distilling at 300-900°C., two to three times weekly for 48 to 65 weeks. Thirty of 35 rats survived the long-continued tar paintings but showed no evidence of tumors." page 46, (4091)

Conflicting results in mouse skin painting experiments. The positive results obtained with tobacco tar skin painting rabbit studies during the 1930's could not be duplicated in mice during the 1930's (3230). An English translation of Taki's presentation during a meeting of the Japanese Society of Pathologists has been obtained:

"Clinically it has been well-known that in smokers there is a high incidence of cancer of the oral cavity, including lip and tongue cancers. Many studies have been conducted to determine whether the cause is mechanical or thermal irritation at the time of smoking, chemical action of tobacco fume or tobacco tar, or a combination of both. In all of these studies on experimental animals, death was induced early through the action of nicotine and other toxic materials contained in tobacco tar, and it has been difficult to demonstrate carcinogenicity of these factors. Some investigators have therefore used nicotine alone or tar from which nicotine has been removed, but these agents have been weakly carcinogenic, and many workers have applied other

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irritants, or have administered hyolesterin or coal tar to increase carcinogenicity. Although there have been a few reports on successful carcinogenesis, they have all been as result of combining other substances. In the mouse, there has not been an instance of success using tobacco tar from which nicotine and other alkaloids have been removed.

We collected tobacco tar and dissolved it in ether, shook the solution with addition of 1% hydrochloric acid to remove nicotine and other alkaloids, washed the preparation with water and dehydrated it with anhydrous sodium sulfate, and removed the ether. This tobacco tar preparation was painted onto the dorsal skin of mice every other day.

In 12 mice that survived for 100 days, one developed an epidermoid tumor and 2 developed papilloma. The animal which developed the epidermoid tumor formed a papillary tumor on about the 60th day which grew to a size of about 1/3 cm. This dropped off, but growth resumed, becoming rapid about the 40th day, to form what appeared grossly to be an epidermoid tumor by the 167th day.

The two cases of papilloma have retained their morphology. One developed around the 40th day and is continuing to grow. We are maintaining these animals to see whether metastasis may occur and to conduct transplantation experiments. Studies are also under way to see whether a tumor may be induced by oral administration of agents in the rat. Although the incidence was low, we succeeded in demonstrating that carcinogen(s) could be shown to be present in material obtained from coal tar." page One, English translation of (3737)

Sugira attempted to replicate Taki's results without success:

"Painting the skin of C57 black mice and dba mice, as well as the ears of rats of Wistar Institute stock and of rabbits of common stock, with tobacco tar failed to produce any cancerous change. The proliferating capacity of mouse sarcoma 180 and the Flexner-Jobling rat carcinoma was unaffected by tobacco tar or pure nicotine solution when the solutions were adjusted to pH 7.4. Another factor which might account for the disagreement between our findings and those of Roffo and Taki is the use of animals of different strains. It is now known that animals of various strains possess marked differences in susceptibility to the carcinogenic action of hydrocarbons. From the fact that only squamous

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carcinoma has been obtained in the course of subjecting a large number of mice to the action of tobacco tar, compared with the very high incidence of cancer in mice treated with coal tar, it seems reasonable to classify tobacco tar as a weak carcinogenic agent." pages 48-49, (4091)

Flory compared the results of tobacco tar with those of coal tar:

"Although the stock mice used in these experiments readily developed squamous cell carcinomas of the skin when painted with coal tar of known carcinogenicity, only 2 squamous cell carcinomas developed as the result of painting animals of the same stock with tobacco tars. Both tumors arose at the sites of painting. One developed after painting with the denicotinized 350-700°C. destructive distillate tar for 8.5 months, the other after 17 months' application of denicotinized pipe tar. Since no similar spontaneous tumors had been seen in some 2,000 of these mice, the production of these squamous cell carcinomas indicated that both tars had a low but definite carcinogenic activity. The earlier time of cancerization, as well as the greater capacity to produce papillomas, indicated that the activity of the 350-700°C. destructive distillate was greater than that of pipe tar. Both tobacco tars were a great deal less active than the potent coal tar used in the control experiments. These observations are in accordance with those of Cooper, Lamb, and Sanders, Campbell, and Siguira, but the work of Taki indicated a higher carcinogenic activity of pipe tar on mice." page 274, (4138)

The above comments were the origin of reference to tobacco tar as less active in potency than coal tar.

Mouse inhalation studies. Lorenz, Stewart, Daniel and Nelson, from the National Cancer Institute, reported negative results in the one of two American publications on inhalation testing of cigarette smoke prior to 1950:

"An automatic tobacco smoking machine was used to expose mice for several hours daily to tobacco smoke. Ninety-seven experimental and 97 control mice (strain A)

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of both sexes were kept in a chamber through which the smoke passed, for from 25 to 250 days. The maximum time was 693 hours. The average smoke content of the air in the chamber was 1mgm. per liter. Calculations gave the amount of tar deposited in the respiratory passages of any one mouse during the entire run as roughly 0.5 gm. No lung tumors were induced by the tobacco tar, for the average number of spontaneous pulmonary tumors was the same in the experimental as in the control animals. Pigmented foci were observed in the lungs of all mice exposed for more than 3 months, probably indicating areas of deposited tar. A few experimental animals showed inflammatory lesions of the stomach and duodenum. Further studies are now in progress." page 123, (4348).

Note: The above article by Lorenze et al and another on inhalation testing are highlight publications.

In a panel discussion during the 1949 National Cancer Conference, the proceedings contained paragraphs suggesting that there was a second American study prior to 1950::

"Experimental studies were reported in which strain A mice were exposed to the inhalation of tobacco smoke for four hours per day for twelve months. No increase in the occurrence of lung tumors was noticed. The tar from such smoke was painted on the skin and injected into the subcutaneous tissues and tar suspensions were injected intravenously and fed without the appearance of tumors in the lung or any other organ during the life span of the animal. It was pointed out that provided oxygen is present, polycyclic hydrocarbons of known carcinogenic activity are not formed on the combustion of tobacco. Oxygen is present in cigarette smoking. A clinical review of 200 case histories of patients with bronchogenic carcinoma was reported suggesting that tobacco smoking is a significant factor in the production of human lung cancer. Lack of time prevented further discussion of this problem." page 203, (4914)

I am attempting to find the laboratory or spokesman for the experimental studies described during the panel discussion.

Rat inhalation study. I have selected this article as a highlight publication. Haag, Weatherby, Fordham & Larson conducted daily life span exposure to cigarette smoke on rats.

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The exposure in a suitable chamber lasted every half-hour, 14 times daily, from weaning age, daily for the entire life span. Compared to cage controls and smoke controls, the smoke exposed rats had no necropsy lesions that were particularly characteristic. Blood pressure determinations taken at regular 2 month intervals showed no differences between the three groups. Weekly weight determinations showed that the cage controls attained and maintained greatest average weight, the smoked exposed groups somewhat less, and the values for the smoked controls being intermediate. The average life span of smoke exposed group was 642 days, smoke controls 544 days, and cage controls 631 days (4667). The exposure level was fixed. As a pioneer effort in inhalation toxicology, the protocol cannot be criticized because determination of maximum tolerated dose was not introduced until two decades later.

#### Irritant Effects of Tobacco Smoke

When this project was reassigned in October 1988, I was requested to avoid any discussion of Harris' statements attributed to cigarette manufacturers. Exhibits consisting of internal reports and correspondence introduced during Harris' deposition and trial proceedings were not available to me, although I read all references relating to his SOA Summary Statement 8, pages 32-27, entitled *Research on Smoking and*

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Health Performed or Sponsored by Cigarette Manufacturers (3460)  
(3464) (3465) (3658) (3667) (3668) (3770) (3671) (4126) (4166)  
(4254) (4367) (4612).

Larsen, Haag & Silvette. I have selected the Tobacco Monograph as a highlight publication because of its excellent summary of the literature on *Irritant Effects of Tobacco Smoke*. Most methods for determining irritation of tobacco smoke were evaluated by the authors at their pharmacology laboratory, Medical College of Virginia. It is difficult to improve on their scholarly description of irritant effects of tobacco smoke. The text starts with the following paragraph:

"The problem of measurement of tobacco-smoke irritation is a most difficult one. Obviously, biological manifestations of irritation must be used and quantitated as best possible. However, the various manifestations are not necessarily interdependent. In consequence, depending on the chemical nature of the irritant, one manifestation of irritation may be affected to a much greater extent than another. Since tobacco smoke is a very complex mixture of substances, which can be varied through changes in the composition of the tobacco smoked, it is apparent that no single biological manifestation of irritation can be used as a complete reliable criterion for evaluating its irritating potency. This does not mean that the various methods proposed for measuring irritation are of no value, but rather that the significance of each must be carefully interpreted and an over-all picture should not be drawn from results obtained by any one method." page 400, (6101)

The opening paragraph was followed by a description of over a dozen clinical and laboratory techniques for measuring mucosal irritation, a characterization of irritation by tobacco constituents, and the influence of hygroscopic agents on irritant

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action. The concluding paragraph was as follows:

"For several years during the 1930's, the controversy between the proponents of diethylene glycol, and those of glycerine, as a humectant for cigarettes was lively and, at times, acrimonious. The conclusions of Mulinos and Osborne and of Flinn as to the relative lack of irritation of diethylene glycol were approved by Clement, Greenwald, and Cone, Hatcher and Greenwald. M. A. Lesser criticized the latter authors for giving a one-sided picture of the value of diethylene glycol as a hygroscopic agent, and for failing to make mention of the adverse literature in this connection. Fishbein then challenged Lesser's qualifications to judge clinical evidence, and pointed out that Lesser in earlier writings had devoted himself largely to encouraging the use of glycerine. Temperately, Bogen briefly reviewed the glycerine-diethylene glycol controversy, and pointed out the necessity for more work. Later, Fabricant extensively reviewed the literature, and concluded: 'Preponderant investigative opinion indicates that there are no differences in the irritating properties of the two types of cigarettes.' The claims made for diethylene glycol have not been substantiated. The experimental evidence appearing since Fabricant's review have borne out his conclusions. Instead of Greenwald's belief that the degree of edema was not influenced by the blend of tobacco or the method of manufacturing the cigarettes, but was purely a function of the hygroscopic agent (and greater for glycerine than for diethylene glycol), the opinion now seems to prevail that neither glycerine nor diethylene glycol significantly alters the irritant properties of cigarette-smoke." page 407, (6101)

There were over sixty references cited by Larsen, Haag & Silvette, and 25 articles were used by Harris in his SOA report.

Justification for research on irritant action of tobacco smoke. My own interpretation of significance of research on irritant action of tobacco smoke is as follows: Since the turn of the century, the most conspicuous pharmacologic effect of tobacco smoke was mucosal irritation, specifically , of the conjunctiva, nose, mouth, pharynx, larynx, and tracheobronchial

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passages. Irritation was not specific for tobacco smoke, but was induced by products of fuel combustion. What was unique for tobacco smoke was the presence of nicotine and this alkaloid was suspected of being the cause of irritation, cardiovascular disease, bronchopulmonary disease, and central nervous system effects.

Tobacco researcher from cigarette companies and medical schools were undoubtedly aware during the 1930's and 1940's that there were publications from Germany, Japan, Argentina, Great Britain and the United States that the majority of lung cancer patients were cigarette smokers. Researchers were also aware that the most widely accepted explanation for pulmonary carcinogenesis was bronchopulmonary irritation. Simon, Hueper and others, as early as 1928, grouped irritants to chemical, bacterial, mechanical, and irradiation. The most prudent approach was to determine ways of reducing irritant action of tobacco smoke. Prior to 1950, that tobacco smoke irritation was a cause of lung cancer was a hypothesis based on a dozen clinical studies, another dozen animal skin painting experiments, and accepted as a fact by two dozen authors. There were also about two dozen authors who were interested in the irritant action of cigarette smoke for the expressed purpose of reducing acute or short-term effects on the ophthalmic, nasal, oral, pharyngeal, laryngeal and broncho-pulmonary mucosa. Whether mucosal irritation also caused chronic diseases was open to question and was

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not necessarily subscribed to by researchers from Virginia, New York, Illinois, Missouri and District of Columbia. The articles listed below were published during the 1930's and 1940's.

Publications from Virginia. Most publications cited by Harris on irritant action of cigarette smoke were either from Philip Morris or the Medical College of Virginia, both of Richmond, VA. The pertinent quotations I selected relate to the expressed purpose of conducting the research, i.e., to reduce acute irritant action of tobacco smoke.

(3559) Greenwald (Philip Morris & Co., Ltd.)

"Due to the great increase in the use of cigarettes and their effects on the mucous membrane of the upper respiratory tract, the causes of irritation and methods for removing some of the irritant properties of smoke have been studied. A series of studies of the blend of tobacco, as well as its method of manufacture, finally pointed to a most surprising fact - that the main source of irritation from cigarette smoke was not the tobacco but the hygroscopic agent. The hygroscopic agent is a substance that is added to tobacco to maintain the moisture content during the course of manufacture. It also serves the important purpose of keeping the finished cigarettes 'fresh' until they reach the hands of the consumer. The hygroscopic agent commonly used is glycerine. It would not seem that glycerine, on first consideration, so generally known as a soothing agent, could have any harmful effects. In cigarettes, however, the glycerine burns with the tobacco - and burning glycerine forms, among other smoke products, a highly irritating and toxic substance. Some hygroscopic agent, of course, is necessary, but it would be preferable to use one which would have the necessary moisture-retaining properties but which on combustion would not produce such an irritant. Such a material, suggested for use as a hygroscopic agent, is diethylene glycol. It has all the desirable properties of a hygroscopic agent but, because of its chemical constitution, cannot on combustion produce an irritant such as that produced by the burning of glycerine. The theoretical advantages of diethylene glycol over glycerine were perfectly

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apparent to the chemist. Before it was possible to be sure that the use of diethylene glycol in place of glycerine made an actual difference in the irritating properties of the smoke, it was necessary to study the smoke itself and its effects. These studies were conducted along pharmacological and clinical lines. ... Tests on rabbit's eyes and on man's nose, throat, mouth and lungs showed conclusively that the irritation caused by smoke from diethylene glycol-treated cigarettes is much less than that from glycerine-treated cigarettes." pages 467-468, (3559)

(3662) Greenwald (Philip Morris & Co., Ltd.)

"Not so long ago, in a summation of our knowledge, it was said that the slight deleterious effects of smoking were not sufficient to overbalance the pleasures to be derived therefrom, with reservations in certain instances of organic disturbance in which the use of tobacco is contraindicated. Numerous conflicting reports of the effects of smoking led to this statement. Whether or not smoking has adverse influences on the vascular system, the lungs, the digestive organs, or on pregnancy, fertility, or growth, or as a possible cause of cancer - are all moot questions. Unfortunately, the effects of smoking constitute a gap in our knowledge and with the exception of the effect of smoking on irritation of the upper respiratory tract, there is much room for study. With the great prevalence of cigarette smoking, there has been an increasing amount of irritation of the upper respiratory tract. Even the various cigarette manufacturers realize this by continuously stressing the mildness of their products (freedom from harsh irritants, throat ease, elimination of coughs, etc.). These improvements are effected by the proper choice of tobaccos and by various methods of treatment of the tobaccos, many of which are 'dark secrets.'" page 366, (3662)

(3772) Cone & Davis (Philip Morris & Co., Ltd.)

"It has been pointed out by Conde that the control of the moisture content of tobacco is one of the most important phases of manufacture. While some hygroscopicity data are available, they are insufficient for the types chiefly used in this country, and the writers had planned additional work to measure the equilibrium vapor pressure of various types, over a wide range of temperatures and moisture values. It was realized, however, that there is no such thing as an 'absolute'

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moisture content for any sample of tobacco; the value obtained depends on the method used, and few laboratories agree on the same method. Methods include drying the samples in ovens, for varying times, at different temperatures, with or without forced air circulation; drying at room temperature over various desiccants, under atmospheric pressure or vacuum; various distillation procedures with solvents immiscible with water; and indirect procedures involving conductivity or dielectric constant. In this work an attempt has been made to compare six methods in common use." page 219, (3772)

(3776) Haag (Medical College of VA)

"When aqueous smoke solutions, obtained from diethylene glycol-treated and glycerin-treated cigarettes, were instilled into the conjunctival sac of rabbits, no differences in the irritating properties of the two types of cigarettes were observed as judged by the appearance of hyperemia, edema, blepharospasm, and the objection of the animal. Likewise, smoke solutions prepared from the two types of cigarettes were found to have the same toxicity upon white mice by intraperitoneal injection." page 346, (3776)

(3777) Haag & Ambrose (Medical College of VA)

"In the rat both diethylene glycol and glycerin lead to an increase in urinary oxalic acid, although it appears that, quantitatively, glycerin is definitely less prone to do so. In the dog, diethylene glycol fed in the amounts reported herein provoked an insignificant increase in the urinary oxalic acid, much of the drug being eliminated unchanged in the urine." page 100, (3777)

(3872) Forbes & Haag (Medical College of VA)

"It would appear, then, that from 7-8 per cent of the total semisolid constituents of smoke consisted of unchanged hygroscopic agent when such material was present in the original cigarette, whether it was glycerol or diethylene glycol. Assuming that these substances were applied in amounts approximating 3 per cent, about 22 per cent of that contained in the tobacco smoked was transferred to the main smoke stream. A similar percentage recovery was obtained for nicotine in the main smoke stream. Results of experiments concerned with the further distribution of nicotine

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during cigarette smoking suggest that most of the remainder of the hygroscopic agent passed into the side smoke stream or was deposited in the butt, as was found to be the case with nicotine. While an elaborate discussion of the toxicology and pharmacology of hygroscopic agents seems hardly within the scope of this paper, it may be noted that even in the case of diethylene glycol the amounts transmitted in the smoke of cigarets are far below those shown to be injurious by oral administration to experimental animals. In what manner the organism would respond to various concentrations of such an agent given by inhalation has never been reported." page 718, (3872)

(4042) Haag (Medical College of VA)

"Employing the blood pressure response as a biological test, it was found that the differences in nicotine content in several brands of cigarettes could be correlated with the effects of solutions prepared from their smoke. Likewise, the toxicity of these smoke solutions by intraperitoneal injection into mice was proportional to their nicotine content. It is concluded that the actions of cigarette smoke solutions, as regards their acute toxicities and their effects on blood pressure by intravenous injection, are due to their nicotine content." page 618, 4042)

(4527) Finnegan, Larson, Haag (Medical College of VA)

"It would seem clear from these results that with many individuals nicotine becomes a major factor in their cigarette habit. Equally certain, with many individuals nicotine is not a factor in their cigarette habit. Even in these individuals in whom nicotine has become a major factor we feel that a cigarette containing no nicotine would be grudgingly accepted as better than no cigarette at all. page 96, (4527)

(4666) Larson, Haag & Finnegan (Medical College of VA)

"We have previously shown both man and the dog that only about 10 per cent of administered nicotine is excreted unchanged in the urine. The fate of the remaining 90 per cent remains to be elucidated. Interpreting this in the light of our findings concerning the fate of nicotine in the animal body, it seems fair to assume that the nicotine metabolite that yields a red color with CNBr is a product of cleavage of the pyrrolidine ring between the nitrogen and the 5 position.

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The additional finding that this substance is not extractable with ether from alkalinized urine is suggestive of the presence of a carboxyl ending on the resulting chain. Whether or not this substance accounts for all or only part of the 90 per cent of administered nicotine that fails to be excreted unchanged, is as yet unknown. pages 239-240, (4666)

(4735) Finnegan, Larsen & Haag (Medical College of VA)

"Neither nicotine nor its products of combustion contribute significantly per se to the edema-producing properties of cigarette smoke, although it may definitely increase the subjective sensations of irritation." page 202, (4735)

(4736) Finnegan, Fordham, Larson & Haag (Medical College of VA)

"1. Tightness of packing of the tobacco within a cigarette can significantly alter the irritant properties of its smoke. The tighter the packing the less irritating is the smoke.

2. The irritant properties of cigarette smoke vary inversely with the moisture content of the tobacco smoked.

3. Cigarettes of the same brand may be of sufficiently uniform composition as to constituents so that no significant difference in irritant properties of their smoke can be detected.

4. The smoke from different brands of cigarettes may differ significantly in irritant properties.

5. The hygroscopic agents, glycerine and diethylene glycol, do not per se significantly alter the irritant properties of cigarette smoke.

6. The irritant properties of cigarette smoke directly applied are markedly greater than those of comparable cigarette smoke solutions." page 123, (4736)

(4760) Larson, Haag & Finnegan (Medical College of VA)

"1. Smoke from different types of cigarette tobaccos may differ significantly in edema-producing irritants. 2. Constituents are present in cigarette smoke, from at least certain types of tobaccos, which produce a degree of subjective irritation disproportionately greater than that which might be expected on the basis of their edema-producing properties." page 478, (4760)

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(4835) Haag, Finnegan & Larson (Medical College of VA)

"It has been shown that a significant decrease of the edema-producing irritants present in cigarette smoke can be effected by (1) limiting the number of puffs taken from a cigarette, (2) increasing the length of the cigarette and limiting the number of puffs taken, (3) attaching a filter tip of suitable design to the cigarette, provided the tobacco column of the cigarette is not correspondingly shortened, and (4) using a cigarette holder containing a changeable filter of suitable design. The practicability of applying these procedures is discussed." page 46, (4835)

Publications from New York. Most of articles were by Mulinos and his collaborators from the Department of Pharmacology, College of Physicians & Surgeons, Columbia University. Their subject was *Influence of Hygroscopic Agents and Acute Irritation by Cigarette Smoke*. Towards the end of the list below, publications from other New York clinics and laboratories are enumerated.

(3463) Mulinos & Osborne (College of Physicians & Surgeons)

"We herewith report a successful attempt to measure objectively the irritant properties of cigarette smoke. We used the conjunctival sac of rabbits according to the technic of Hirschhorn and Mulinos. Cigarettes made with 1,3, and 5% glycerine respectively show a slight increase in irritation as the percent of glycerine increases. When di-ethylene-glycol is used, there is a slight but readable reduction in irritation as the percent increases. When the cigarette smoke is passed through mineral oil, the results are essentially the same as when water is used." pages 241, 245 (3463)

(3564) Mulinos & Osborne (College of Physicians & Surgeons)

"The irritation produced by cigarette smoke should be of great importance to the physician who has under his care the treatment of affections of the nose and throat. Offhand, it is rather difficult to place a definite value upon the importance of cigarette smoke in the production and perpetuation of these throat condi-

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tions. For any one patient, however, we may assume that cigarette smoke may play some part in the pathology of the throat condition for which he has consulted his physician. The source of the tobacco, the flavoring agents, or the paper may each play its part in the qualities of the smoke. But besides these constituents of all cigarettes, there is another which has proved of interest. All cigarettes contain some agent for the maintenance of the proper moisture content of the tobacco. The present study is aimed at the two popular hygroscopic agent, glycerine and diethylene glycol, and their influence upon the irritant properties of cigarette smoke. Cigarettes identical in every other respect vary in irritating properties of their smoke, according to the type of hygroscopic agent used. Cigarettes in which glycerine is used are more irritating than when no hygroscopic agent is employed, while those made with diethylene glycol are definitely less irritating. Our results now show that, regardless of the blend of tobacco, flavoring materials, or method of manufacture, the irritation produced when glycerine is used as the agent is substantially the same - and greater than that caused by diethylene glycol.

Although these results apply only to our method of smoking the cigarettes, and to aqueous or oily solutions of the smoke, and although the irritation is measured upon the conjunctival mucous membrane of rabbits, the investigations of Flinn in 1935 indicate that the same relative irritation produced by these two hygroscopic agents holds also for the human cigarette smoker." pages 590-592, (3563)

(3664) Lieb, Mulinos & Taylor (College of Physicians & Surgeons)

"These experiments suggest that the vasoconstriction from a deep breath occurs on the arterial side of the capillary tuft, a fact borne out also by the marked changes in temperature of the skin. They suggest also that the phenomenon is of neural or reflex origin, and is not due to mechanical shifts of blood into the pulmonary circulation, for such shifts are prevented by the circulatory occlusion induced. Skin temperatures taken during a deep breath show a drop of from 1°C. to 3°C. Several deep breaths taken at one-minute intervals show a summation of effect, and a drop in from 1°C. to 6°C. That this can occur is denied specifically by Wright and Moffat, and implied by Maddock and Collier. The reflex mechanism has not yet been analyzed further, but may be due to one or more of such factors as alveolar stretching; to vascular reflex from pulmonary

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blood pressure changes; or to the cooling effect of the inspired air." page 90, (3664)

(3785) Kesten, Mulinos & Pomerantz (Coll. Physicians & Surgeons)

"A report of several fatalities following the use of an 'elixir' of sulfanilamide made with diethylene glycol prompts this preliminary abstract of a portion of the work in progress on the pharmacology and pathology of the glycols and related chemicals. Only two studies of the toxicity of diethylene glycol appear in the literature. Von Oettingen and Jirouch found, using four mice, that minimum lethal dose was approximately 5 cc. per kilogram of body weight when given subcutaneously. Haag and Ambrose reported that the ingestion of the glycol in concentrations of 3 per cent and 10 per cent in drinking water was rapidly fatal to rats and that the minimum fatal dose for rabbits is 2 cc. intravenously. The vital organs of these animals were found to be essentially normal.

Diethylene glycol, administered to rats by mouth and to rabbits intravenously, caused extensive injury to the epithelium of the renal convoluted tubules, leading to urinary obstruction and uremia. The liver and adrenal were less regularly involved. A dose of from 1 to 2 cc. per kilogram of body weight intravenously to rabbits was required. The ingestion by rats of 0.5 and 1 per cent solutions in their drinking water in quantities of approximately 30 cc. daily per rat for from one to four or five months caused no renal or other symptoms. Three per cent (0.9 cc. per rat daily) in drinking water killed about 50 per cent of the rats within two months. Five per cent diethylene glycol (1.5 cc. per rat daily) killed 25 per cent within a week." pages 150-151, (3785)

(3875) Mulinos & Cockrill (Coll. Physicians & Surgeons)

"Studies were made on the smoking of cigarettes by means of a mechanical puffer under standardized conditions. It has been shown that cigarette tobacco acts as an efficient filter in respect to total volatile substances; solids; reducing substances to iodine solution; nicotine; acidity, (hydrogen ion concentration); and the color and clarity of the smoke solution. If the cigarette smoker does not smoke more than 2 thirds (5 cm.) of the cigarette, he avoids all changes in temperature of the smoke, and 60 to 70 per cent of the nicotine, tarry substances, acids, and volatile substances which reduce iodine." page 206, (3875)

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